could demonstrate in TEN-HMS. We had no learning period to identify appropriate triggers and responses to the new information being acquired. The analyses they request are only now being done; the techniques required are complex to apply. We also agree that remote telemonitoring by people who have little knowledge of the patient and who are not in a position to offer practical help if needed is unlikely to be optimal. Telemedicine that integrates care at the local and regional level is most likely to meet with success.

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REFERENCES

1. Cleland JG, Louis AA, Rigby AS, Janssens U, Balk AH. Noninvasive home telemonitoring for patients with heart failure at high risk of recurrent admission and death: the Trans-European Network–Home-Care Management System (TEN–HMS) study. J Am Coll Cardiol 2005;45:1654–64.
2. Cleland JGF. How to assess new treatments for the management of heart failure: composite scoring systems to assess the patients' clinical journey. Eur J Heart Fail 2002;4:243–7.
3. Abraham WT, Fisher WG, Smith AL, et al., for the MIRACLE Study Group. Cardiac resynchronization in chronic heart failure. N Engl J Med 2002;346:1845–53.
4. Goldberg LR, Piette JD, Wals MN, et al., on behalf of the WHARF Investigators. Randomized trial of a daily electronic home monitoring system in patients with adavanced heart failure: the Weight Monitoring in Heart Failure (WHARF) trial. Am Heart J 2003;146:705–12.
5. GESICA Investigators. Randomised trial of telephone intervention in chronic heart failure: DIAL trial. BMJ 2005;331:425–30.

Pleiotropic Effects of Statins and Early Benefit in the PROVE IT–TIMI-22 Study

Ray et al. (1) discuss the early and late benefits of 80 mg/day of atorvastatin in the acute coronary syndrome patients of the PROVE IT–TIMI-22 (Pravastatin or Atorvastatin Evaluation and Infection Trial–Thrombolysis In Myocardial Infarction-22), and they conclude that the early benefit observed in this trial is likely due to the pleiotropic effects of the statin used.

Conversely, the difference in the triple end-point incidence they observe after 30 days, as can be seen in Table 1 of their study, is limited to patients with plasma low density lipoprotein (LDL) cholesterol levels ≥125 mg/dl at randomization (hazard ratio [HR] 0.31; 95% confidence interval [CI] 0.15 to 0.64; $p < 0.002$), whereas it is completely absent in patients with LDL cholesterol <125 mg/dl at randomization (HR 0.92; 95% CI 0.63 to 1.36; $p = 0.7$). It is intriguing that a purported nonlipidic effect of a statin is observed only in patients with elevated LDL cholesterol. Pleiotropic effects should, conceptually, exert their protective properties at any lipid level.

Attribution of the early protective action observed in the PROVE IT–TIMI-22 trial to the pleiotropic effects of the statin used should be, in our opinion, more cautious. In actuality, a clear demonstration of the clinical relevance of these effects is still lacking. A recent meta-regression of published clinical trials testing different hypolipidemic treatments concludes that cholesterol reduction is likely to be the major (or unique) determinant of coronary heart disease and stroke events reduction (2).

Indeed, LDL reduction obtained by a single LDL apheresis markedly reduces C-reactive protein and ameliorates the endothelial function of coronary arteries (3), suggesting that LDL reduction, by itself, can rapidly translate into a variety of biochemical or clinical benefits. Perhaps we should abandon the concept of "pleiotropic effects of statins" in favor of that of "pleiotropic effects of cholesterol reduction."

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REFERENCES

1. Ray KK, Cannon CP, McCabe CH, et al. Early and late benefits of high-dose atorvastatin in patients with acute coronary syndromes: results from the PROVE-IT–TIMI-22 trial. J Am Coll Cardiol 2005;46:1405–10.
2. Robinson JG, Smith B, Maheshwari N, Schrott H. Pleiotropic effects of statins: benefit beyond cholesterol reduction? A meta-regression analysis. J Am Coll Cardiol 2005;46:1855–62.
3. Igarashi K, Tsuji M, Nishimura M, Horimoto M. Improvement of endothelium-dependent coronary vasodilation after a single LDL apheresis in patients with hypercholesterolemia. J Clin Apheresis 2004;19:11–16.

REPLY

We thank Drs. Poli and Pujia for their interest in our report (1). They suggest that the more significant reduction in clinical events observed among patients with a high low-density lipoprotein cholesterol (LDL-C) versus those with a low LDL-C at baseline provides evidence that the early benefits observed at 30 days are related more to lipids than any potential pleiotropic effects. Acute coronary syndrome (ACS) patients have a high early recurrence of adverse events after ACS. The significant early benefits of intensive statin therapy observed by day 30 in the PROVE IT–TIMI-22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction-22) trial seem more striking when compared to the benefits of intensive LDL-C reduction by ileal bypass in the POSCH (Program on the Surgical Control of the Hyperlipidemias) study, which took nearly seven years to translate into clinical benefit (2). Similarly, in the early statin trials in stable coronary artery disease (CAD) the benefits of statins were observed after one to two years, suggesting that in stable patients the benefits of modest reductions in LDL-C take place over a period of years rather than days. Whereas we agree that LDL-C reduction itself is associated with reductions in C-reactive protein (CRP) and endothelial function, we have demonstrated that, independent of achieved LDL-C and other correlates,

the dose of the statin regimen is a significant determinant of CRP levels (3).

Several lines of evidence also suggest that the pleiotropic effects of statins may be as relevant as the LDL-C–dependent effects with respect to clinical outcomes (4). Comparisons across other ACS trials provide further insight into the potential mechanisms of early benefit. For instance, in the A to Z trial (5), there was a greater LDL-C differential between intensive and moderate statin regimens than in the PROVE IT–TIMI-22 trial. However, unlike the PROVE IT–TIMI-22 trial, there was no difference in CRP at 30 days between treatments in the A to Z (Aggrastat-to-Zocor) study and also no early benefit was observed. Similarly, in the MIRACL (Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering) study the benefit of intensive statin therapy at four months was independent of the baseline and six-week LDL-C (6). Taken together these data suggest that mechanisms other than LDL-C reduction may contribute to early benefit. The recent meta-regression that Drs. Poli and Pujia refer to did not include ACS patients, and it is therefore unclear whether it is applicable to an ACS population during a short follow-up.

Finally, in an additional analysis among patients alive at day 30 with LDL-C data available in the PROVE IT–TIMI-22 trial, we observed that the benefits of intensive statin therapy at reducing myocardial infarction or recurrent ACS in the previous 30 days were present irrespective of whether LDL-C was above or below the median at day 30 after adjustment for age, gender, and diabetes, providing further support for the hypothesis that mechanisms beyond intensive LDL-C reduction may play a role in the early benefits observed (Fig. 1).

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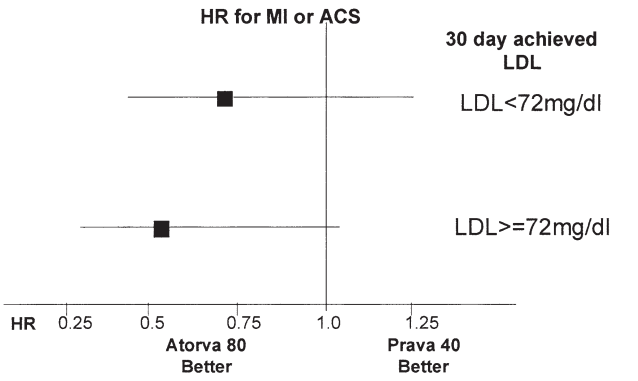

Figure 1. Risk of myocardial infarction (MI) or recurrent acute coronary syndrome (ACS) within 30 days of index ACS stratified by median day-30 low-density lipoprotein (LDL) cholesterol. HR = hazard ratio.

REFERENCES

1. Ray KK, Cannon CP, McCabe CH, et al. Early and late benefits of high-dose atorvastatin in patients with acute coronary syndromes: results from the PROVE IT–TIMI-22 trial. J Am Coll Cardiol 2005;46:1405–10.
2. Buchwald H, Varco RL, Matts JP, et al. Effect of partial ileal bypass surgery on mortality and morbidity from coronary heart disease in patients with hypercholesterolemia. Report of the Program on the Surgical Control of the Hyperlipidemias (POSCH). N Engl J Med 1990;323:946–55.
3. Ray KK, Cannon CP, Cairns R, et al. Relationship between uncontrolled risk factors and C-reactive protein levels in patients receiving standard or intensive statin therapy for acute coronary syndromes in the PROVE IT-TIMI 22 trial. J Am Coll Cardiol 2005;46:1417–24.
4. Ridker PM, Cannon CP, Morrow D, and the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22) Investigators. C-Reactive protein levels and outcomes after statin therapy. N Engl J Med 2005;352:20–8.
5. De Lemos JA, Blazing MA, Wiviott SD, et al. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. JAMA 2004;292:1307–16.
6. Olsson AG, Schwartz GG, Szarek M, et al. High-density lipoprotein, but not low-density lipoprotein cholesterol levels influence short-term prognosis after acute coronary syndrome: results from the MIRACL trial. Eur Heart J 2005;26:890–6.